

High-Field *in vivo* Visualization of the Human Globus Pallidus Using 7T MRI

Abstract

In the past several decades the introduction of high-resolution, three-dimensional modeling techniques have revolutionized our ability to visualize the human brain and its connectivity patterns between structures. The use of high-field magnetic resonance imaging (MRI) offers promising applications in advancing therapeutic strategies for a wide range of neurodegenerative diseases. Deep brain stimulation (DBS) surgery is one such strategy used in the treatment of patients with neurological movement disorders such as Parkinson disease (PD), essential tremor, and dystonia, involving the degeneration of basal ganglia circuits.¹ For patients with moderate-to-advanced Parkinson disease, in which drug therapy is no longer sufficient, the globus pallidus interna (GPi) and subthalamic nucleus (STN) are targets for DBS², however, there has been debate on whether unilateral GPi or STN DBS is more effective as a therapeutic strategy for patients with moderate-to-advanced Parkinson disease. Recent research suggests that stimulation of GPi in DBS is a better therapeutic approach as the GPi is a much larger structure and does not require the same degree of precision for placement of DBS lead as

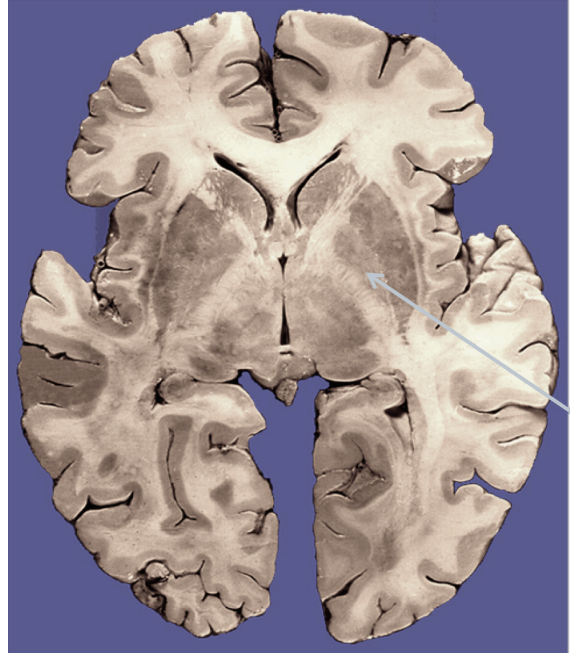
compared to STN DBS. Furthermore, the GPi is also less susceptible to damage following insertion of the DBS lead compared to the smaller STN target, which likely has a large role in cognitive dysfunction post-DBS.³ Thus GPi DBS may be a safer strategy for therapeutic treatment of patients with moderate-to-advanced Parkinson disease.

Introduction

The globus pallidus is structurally divided into two parts, the globus pallidus interna (GPi) and the globus pallidus externa (GPe), which are separated by a thin layer termed the lamina pallidi medialis. For patients with Parkinson disease, the GPi is a target for DBS surgery. Most DBS surgeries still heavily rely on atlases constructed from *post-mortem* specimens that are superimposed on a patient's MRI scan, an indirect-targeting method still prevalent to this date. Patient-specific, three-dimensional mapping of structures within the basal ganglia core through the use of high-field magnetic resonance imaging may prove to be a valuable pre-operative tool in providing important information for the planning of DBS surgery and targeting specific structures.

Due to the variability in the location of basal ganglia nuclei among human subjects and small target structures which generally measure less than 10 mm in most dimensions⁴ for the placement of DBS electrodes, comprehensive patient-specific mapping of the globus pallidus using high-field MRI scans of individuals could provide surgeons with significant pre-operative information for DBS surgery planning.^{5,6} Patient-specific visualization of the globus pallidus could provide higher success rates for DBS procedures as the success of such surgical procedures are heavily dependent on the accurate placement of DBS electrodes into the target region of the brain. Reducing the need for multiple microelectrode recording (MER) penetrations during GPi DBS surgery, detailed mapping of the globus pallidus could also serve to minimize the procedural risk of intracranial hemorrhage and damage to axonal tracts.⁴ Furthermore, patient-specific information could have a significant impact on the outcome of a much greater number of DBS treatments as the indications for DBS surgeries are expected to increase significantly in the near future.⁶

By visualizing the globus pallidus *in vivo* using high-field 7-Tesla MRI scans with T2 contrast of individual human subjects, the procedural



- Figure 1 – Axial cross-section of adult brain specifying location of the globus pallidus

applications of comprehensive patient-specific mapping of the globus pallidus can be validated.

The research question addressed in this study was whether gender-specific volumetric differences exist in the globus pallidus in patients with moderate-to-advanced Parkinson disease. It is known that the overall head size of males are typically larger than that of a female, however, subcortical structures seem to have similar sizes. Based on this knowledge it was hypothesized that there would be no evidence of volumetric differences in the globus pallidus between male and female patients with Parkinson disease.

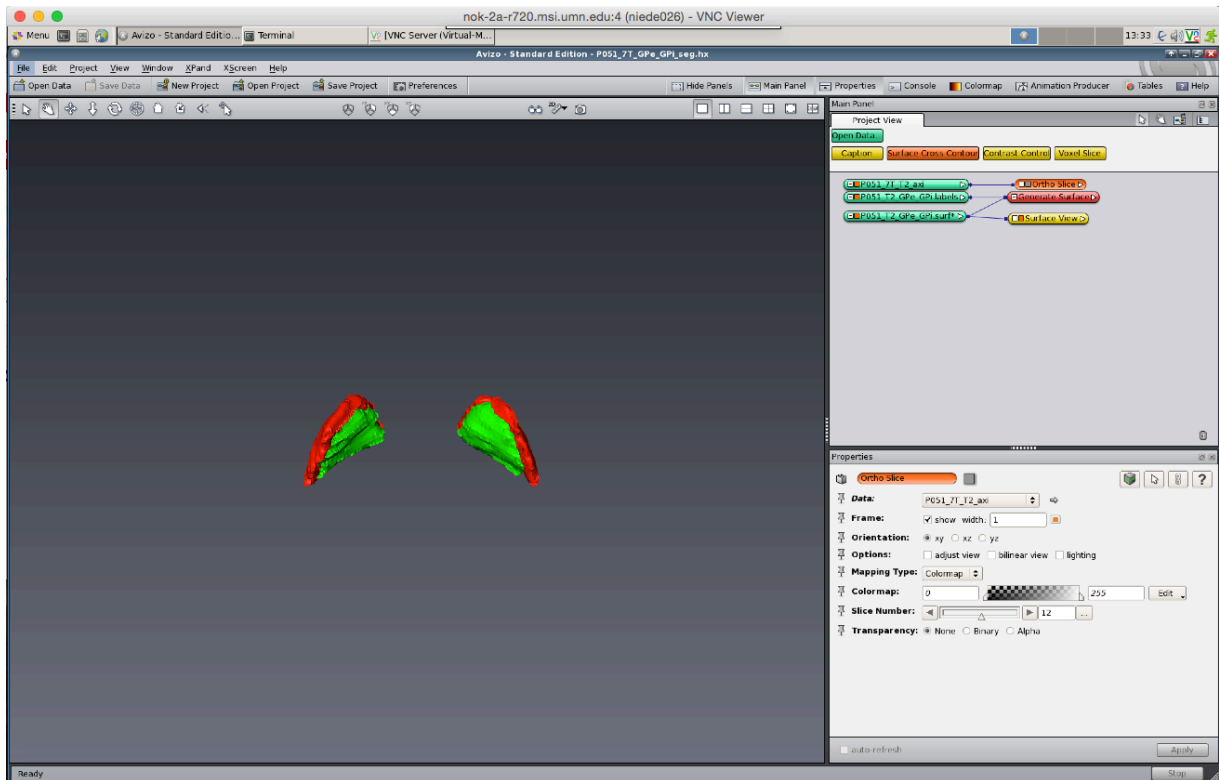
Materials and Methods

To investigate whether volumetric differences exist between male and female patients with moderate-to-advanced Parkinson disease, the three-dimensional software platform Avizo (FEI Software, Hillsboro, Oregon) was used for the visualization, manipulation, and analysis of patient data. Using the program, segmentations of the GPi and GPe borders of 50 patients with moderate-to-advanced Parkinson disease were completed to construct three-dimensional patient-specific representations of the globus pallidus used for quantitative volumetric

analysis. Refer to *Figure 2* for a representation of an axial section of the globus pallidus segmented in Avizo, in which GPi has been labeled green and GPe has been labeled red. Following the segmentation of each axial slice of the globus pallidus, a three-dimensional patient-specific representation of the structure could be generated, from which volumes for GPi and GPe could be determined and used for statistical analysis. Refer to *Figure 3* for a three-dimensional patient-specific surface view of the globus pallidus generated from axial segmentations of GPi and GPe borders.



- Figure 2 – Defining the border of bilateral globus pallidus with label field editing Avizo software



- Figure 3 – Three-dimensional visualization of bilateral globus pallidus in Project View of Avizo

Results

From the segmentation data bilateral GPi and GPe volumes were extracted from Avizo and used to calculate the average volumes and standard deviations for each data set. GPi_L (left) average volume for all patients was found to be 529 mm^3 ($\text{SD} = 122 \text{ mm}^3$), as compared to an average volume of 575 mm^3 ($\text{SD} = 125 \text{ mm}^3$) for GPi_R (right). Average volumes for GPe_L and GPe_R were found to be 888 mm^3 ($\text{SD} = 197 \text{ mm}^3$) and 885 mm^3 ($\text{SD} = 175 \text{ mm}^3$), respectively. Average total volume for globus pallidus was found to be $2,876.97 \text{ mm}^3$ with a

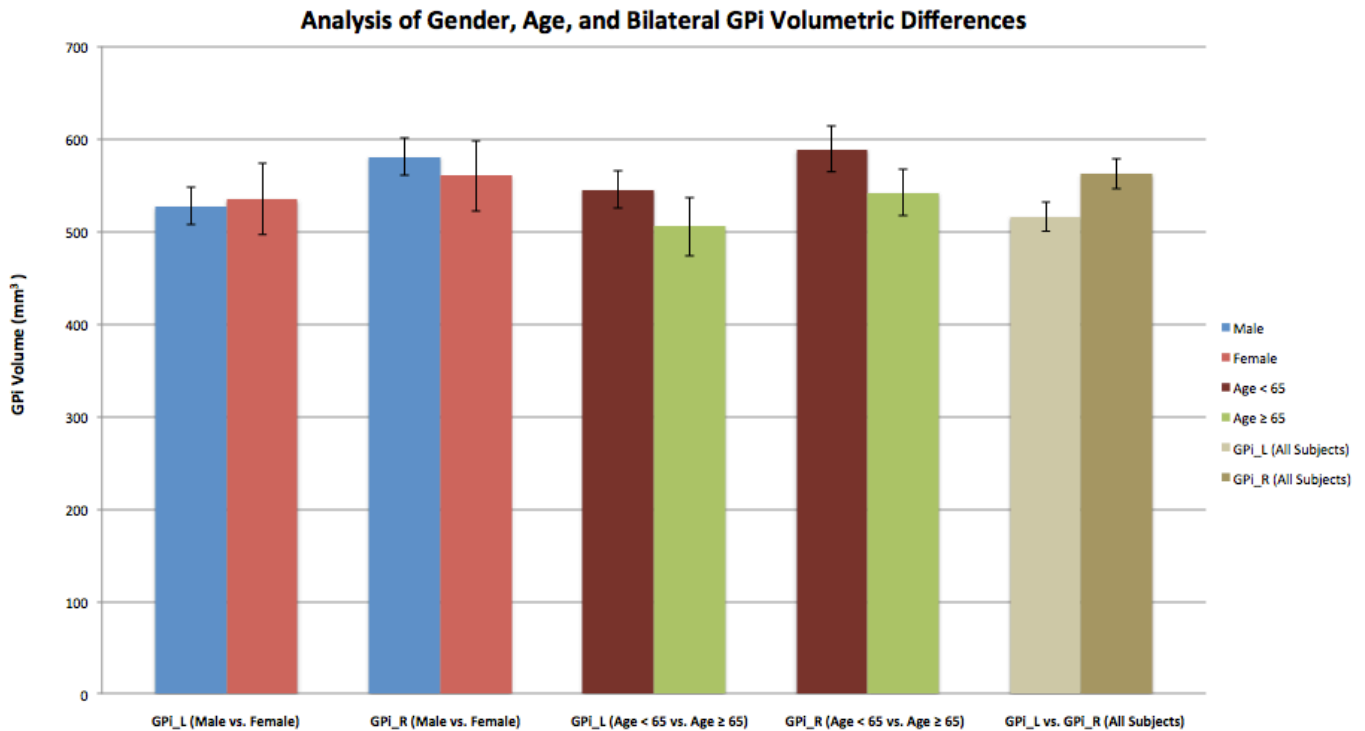
standard deviation of 466.52 mm^3 . This value for total globus pallidus volume was larger than literature values for globus pallidus volume of control subjects, which are given in *Table 1*. Volumetric analysis of GPi and GPe is still a relatively new area of research with the advent of high-field magnetic resonance imaging techniques that allow for increased resolution and identification of structural landmarks.

A two-tailed two-sample t-test was used to determine whether a significant difference in GPi volume exists between male and female subjects. In this test, volumetric data for 11 female

Source	Total GP_L Volume	Total GP_R Volume	Total GPi Volume	Total GPe Volume	Total GP Volume
7T Patient Data	1417.09	1459.88	1104.23	1772.74	2876.97
Spinks, et al. ⁷	Not Measured	Not Measured	1180	2490	3660*
Hokama, et al. ⁸	1150	1110	Not Measured	Not Measured	2260
Peterson, et al. ⁹	Not Measured	Not Measured	Not Measured	Not Measured	1762.3
Hopkins, et al. ¹⁰	Not Measured	Not Measured	Not Measured	Not Measured	2340
Harris, et al. ¹¹	Not Measured	Not Measured	Not Measured	Not Measured	2060

- Table 1 – Average volumes for all subjects in the 7T DBS patient data set were measured and compared with literature volumes for globus pallidus (all volumes reported in mm³)

*The reported volume of 3,660 mm³ for total globus pallidus was regarded as an outlier



- Figure 4 – Summary of gender-specific, age-specific, and bilateral volumetric differences in GPi (error bars represent the standard error for each data set)

subjects were compared with data for 36 male subjects. Three subjects from the patient data set did not have a specified gender and were excluded from the sample t-test. In order to compare independent groups of unequal sample size, the Satterthwaite approximate was used to determine the degrees of freedom (df) needed to calculate the probability value (p-value). The results of the t-test confirmed the null hypothesis that no significant gender-specific volumetric differences in GPi exist in patients with moderate-to-advanced Parkinson disease. Large p-values ($p > 0.5$) were observed for unilateral GPi differences between genders, indicating that volumetric differences observed in the sample of male and female patients were statistically insignificant ($p = 0.863$, $df = 16$ for GPi_L and $p = 0.643$, $df = 16$ for GPi_R).

In addition to testing for gender-specific differences in volume, another two-sample t-test was performed to test for age-related volumetric differences in the GPi. Subjects were divided into one of two groups, the first consisting of 28 patients younger than 65 years and the second consisting of 19 patients 65 years and older. The same three patients excluded from the gender-specific t-test were excluded from the age-specific t-test due to unspecified age. Again, the

Satterthwaite approximate was used to determine degrees of freedom for the two groups.

Although much smaller p-values were observed, the results of the t-test indicated that no significant age-specific differences in unilateral GPi volumes exist between the two groups tested ($p = 0.297$, $df = 38$ for GPi_L and $p = 0.112$, $df = 35$ for GPi_R). A statistical significance level of 0.05 ($p < 0.05$) is generally needed to infer statistical significance for a given set of data.

Although it was concluded that there was no statistical evidence to indicate gender or age-specific differences in GPi volume, a paired t-test comparing GPi_L and GPi_R for all patients yielded an unexpected result. The mean volume of GPi_L for all patients was 529 mm^3 ($SD = 122 \text{ mm}^3$), whereas the mean volume of GPi_R for all patients was 575 mm^3 ($SD = 125 \text{ mm}^3$). Thus, GPi_R was determined to be an average of 8.70% larger than GPi_L. To test whether this observation was statistically significant, a one-tailed paired t-test was performed to determine if GPi_R is significantly larger in volume than GPi_L in patients with moderate-to-advanced Parkinson disease. The t-test yielded a very low p-value ($p < 0.01$) indicating, for the patient data set tested, GPi_R volume was significantly larger than GPi_L volume.

($p = 0.00415$, $df = 49$). This finding was not replicated for GPe, in which another paired t-test (one-tailed) was performed yielding a much larger p-values ($p = 0.439$, $df = 49$). It was determined that differences in bilateral GPe were statistically insignificant. A final one-tailed paired t-test was performed to determine whether whole GP_R was significantly larger in volume than whole GP_L. Although whole GP_R was observed to be an average of 3.02% larger in volume than whole GP_L from the patient data set, this difference was determined to be statistically insignificant ($p = 0.0674$, $df = 49$). Refer to *Figure 4* for a summary of gender-specific, age-specific, and bilateral volumetric differences of GPi in patients with moderate-to-advanced Parkinson disease.

Discussion

Following statistical analysis of measured GPi volumes in patients with moderate-to-advanced Parkinson disease, it was determined that there was no evidence to support any gender-specific volumetric differences in the globus pallidus. This finding was consistent with previous knowledge that subcortical structures appear to have similar sizes despite differences in average head size between genders. In addition, there

was no evidence of any age-specific differences in GPi volume when comparing patients younger than 65 years to patients 65 years and older.

A possible explanation for the larger volumes observed from the Avizo segmentations using high-field 7T patient data as compared with referenced literature volumes in *Table 1* is a phenomenon known as the partial volume effect. Partial volume effect can be described as the limited ability to clearly identify anatomical borders due to low resolution. Today's 1.5 Tesla MRI machines used in clinical settings generate patient data with a greater space between axial slices, compared with patient data obtained at 7 Tesla (2-3 mm in 1.5 T compared to 1 mm in 7T). This difference may result in the apparent loss of volume in brain structures imaged at lower magnetic fields. The advantage that high-field magnetic resonance imaging provides is increased resolution and greater contrast of structural borders. This allows for the improved ability of defining structures in the brain and generating accurate three-dimensional representations.

The finding that GPi_R was significantly larger in volume than GPi_L from the data set of patients with Parkinson disease may have numerous procedural applications, providing

surgeons with valuable pre-operative information useful for DBS surgery planning. Knowledge of volumetric differences between GPi_L and GPi_R prior to surgery could impact the pre-operative planning for the placement of DBS lead in the GPi structure. In addition, taking into account patient-specific information prior to surgery could help to improve the success rate of DBS operations.

Although it was statistically determined that GPi_R was significantly larger in volume than GPi_L for the patient data set, it is important to note that there was also a significant amount of variance in measured patient GPi volumes. This variance can be quantified by Cohen's d size effect. A Cohen's d size effect greater than 0.5 is generally used to infer that the statistical power of a data set is moderate, whereas a size effect greater than 0.8 is used to infer strong statistical power. The size effect for the patient data set was calculated to be 0.425, indicating that the statistical power of the data could be improved. The lower the size effect, the more likely observed findings may be erroneous and attributable to chance. One approach to improving the size effect would be to analyze a larger sample of patient data to lower the variance in measured volumes. Improving the

statistical power of the patient data in this study would help to validate the finding that GPi_R is indeed larger in volume than GPi_L in patients with moderate-to-advanced Parkinson disease.

Conclusion

This work helps to define the volumetric differences of the globus pallidus in patients with moderate-to-advanced Parkinson disease.

Although there is no evidence of gender or age-specific differences in globus pallidus volume, there is significant evidence to suggest that GPi_R is larger in volume than GPi_L in patients with Parkinson disease. The potential causes for this difference are still unclear and is a future avenue of research. Further research is needed to replicate these findings and confirm the validity of apparent volumetric differences in bilateral GPi in patients with moderate-to-advanced Parkinson disease.

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